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MEDICAL STAFF CONFERENCE

Manifestations and Treatment of Acromegaly

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* We are very fortunate to have Dr. Seymour Levin with us today to discuss the manifestations and treatment of acromegaly.

DR. LEVIN:† It has been 85 years since Marie's[1] description of acromegaly and 45 years since Davidoff's[2] detailed review of the clinical findings in 100 patients seen at the Peter Bent Brigham Hospital from 1913 to 1926. Davidoff's study remains one of the most valuable analyses of the disease though published in an age in which treatment of this condition was just beginning. I would like to review with you some of our clinical findings and compare them with those of Davidoff. In addition, I will discuss metabolic studies in 50 patients before and after cryohypophysectomy, the major form of treatment now used at the University of California, San Francisco.

Acromegaly is a disease which is the result of the chronic effects of excessive pituitary growth hormone (somatotropin) secreted during adult life. It is of interest that the Davidoff studies, and collaborative surgical and pathological studies with Harvey Cushing, were done at the same time growth-producing properties of the pituitary were being discovered at this school by Evans and Long.[3] Table 1 compares the clinical data in Davidoff's patients with those in our series. The sex distribution and age are surprisingly similar. The shorter duration of symptoms in our patients is probably the result of earlier detection today.

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Symptoms

The symptoms reported in the two series are shown in Table 2, arranged according to the time sequence of appearance. The earliest symptoms are of a nonspecific nature. Cosmetic changes are often apparent to others, but not to the patient until later. The more frequent occurrence of sexual dysfunction in the Davidoff series, as compared with our study, is probably related to longer duration of the disease in their patients.

Paresthesias are an early symptom and may result initially from metabolic effects of growth hormone upon the nerves[4] rather than from an entrapment of the median nerve (carpal tunnel syndrome) which occurs later in the illness. Figure 1 shows a patient at 25 years of age. At that time she noted some tingling of her hands, but did not see a physician. Her features, however, were suggestive of very early acromegaly. Over the years she experienced fatigue; but it wasn't until six months ago, at the age of 46

TABLE 1.—*Clinical Review of Acromegaly*

	Davidoff (1926)	*Present Study (1971)*
Number of Patients	100	50
Sex	44% M, 56% F	50% M, 50% F
Mean Age	Slightly over 40 years	42 (21 - 65) years
Duration of Symptoms	About 15 years	9.6 years

TABLE 2.—*Symptoms in Acromegaly*

	Davidoff (1926)	*Present (1971)*
Earliest		
Fatigue or Lethargy	42%	82%
Paresthesias	30%	62%
Amenorrhea	73% of females	32% of females
Headache	87%	64%
Later		
Excessive Perspiration	60%	88%
Weight Gain	39%	76%
Photophobia	12%	46%
Acral Enlargement	100%	96%
Voice Change	?	50%
Decreased Libido	38%	27%
Late		
Joint Pain	?	76%
Cardiac Symptoms	?	12%

TABLE 3.—*Signs in Acromegaly*

	Davidoff (1926)	*Present (1971)*
Acral Changes	100%	96%
The Warm, Moist, Fleshy, Handshake	?	96%
Hypertension	?	23%
Goiter	25%	18%
Lactation	4%	8%
Dermal Changes		
Fibromata Mollusca	27%	38%
Acanthosis Nigricans	?	26%

(Figure 1), that her headache became so severe that she sought help, and the diagnosis of acromegaly was made. Besides cosmetic deformity, she was found to have suprasellar extension of the pituitary tumor, glucose intolerance, early heart failure, lactation, and hypertrophic arthritis. Earlier detection and treatment might have avoided this extreme progression of the disease.

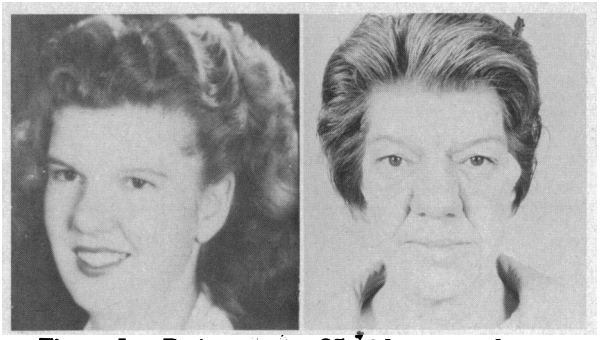

Figure 1.—Patient at age 25 with very early symptoms, and at age 46 with late symptoms and signs of acromegaly.

Physical Signs

The physical signs of acromegaly were quite similar in the two series (Table 3). However, Davidoff did not mention the warm, moist, fleshy handshake, reflecting hypermetabolism and increased soft tissue mass, which we consider so characteristic of acromegaly.

Lactation was present in two males and two postmenopausal females in our series. Lactation may occur in many types of pituitary disorders.[5] It is often not noted by the patient and requires proper examination by the physician to extrude some milk. A gentle, para-areolar pressure is followed by a symmetrical, firm rolling movement of the nipple with the sides of the thumbs (Figure 2). Large tumors which have been present for a long time appear most likely to be associated with the presence of lactation. Inhibition of prolactin inhibitory factor (PIF) in the hypophyseal stalk is probably responsible for lactation in patients with pituitary tumors. Reduced secretion of PIF is thought to allow for the release of pituitary prolactin and subsequent lactation. In addition, growth hormone itself may have some lactogenic effects.[6,7]

Of the skin changes, acanthosis nigricans has been of interest to us, since we have seen it in six of our last 23 patients. Microscopic skin folding and increased pigment produce a dark, carpet-like texture to the skin in the axillae (Figure 3). It may provide an important clue to the existence of acromegaly, as well as other pituitary tumors.[8] Controversy exists as to whether in acromegaly the lesion should be called "pseudo"-acanthosis nigricans, a condition which occurs in areas of excessive sweating and pressure and is identical histologically with true acanthosis ni-

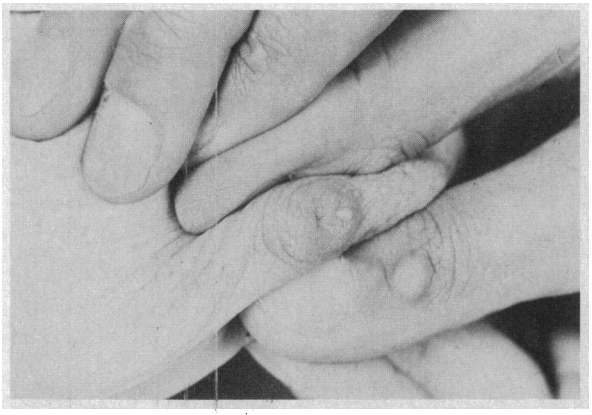

Figure 2.—Demonstration of galactorrhea by gentle extrusion of milk, using a rolling motion with the thumbs.

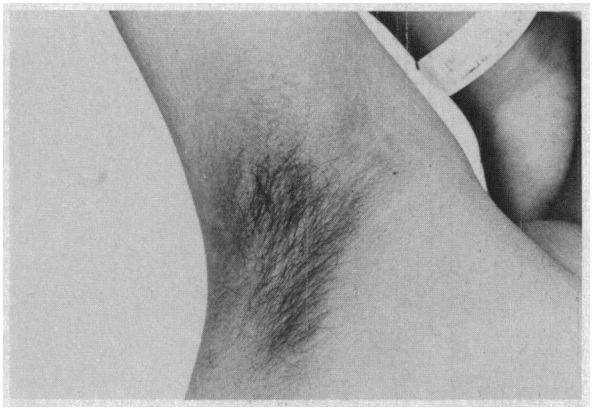

Figure 3.—Acanthosis nigricans in a patient with acromegaly.

gricans. We have, however, seen this skin lesion in patients with acromegaly who were not sweating excessively and did not have thickened skin.

Radiological Signs

Davidoff[2] reported radiographic demonstration of an enlarged sella turcica in 93 percent of his patients, while we have seen this condition in 90 percent of our patients. This finding is often accompanied by enlarged frontal sinuses, hyperostosis frontalis, and enlarged mandible (Figure 4). Most of these changes are the result of remodeling of bone due to proliferative changes in cartilage.

Soft tissue thickening of the hands and an enlarged sesamoid bone (Figure 4) are frequently present. An increased sesamoid index,[9] that is, greatest longitudinal diameter times greatest horizontal diameter of the thumb sesamoid bone (upper limit of normal is 29 mm), is probably not as reliable a sign as is the heel pad thickness. Steinbach[10] reported eight years ago that the best radiological sign is a thickened heel pad. This is the shortest vertical distance from the calcaneus to the volar surface of the foot (Figure 4). Ninety-eight percent of our patients have heel pad thickness over 22 mm, which is considered the upper limits of normal.

All of our patients had pneumoencephalography (PEG) to delineate the upper limits of the pituitary gland. A recently appreciated radiological finding is the "empty sella syndrome"[11,12] which was seen with the PEG in 8 percent of our patients. This condition represents an abnormal extension of the subarachnoid space downward into the sella, so that air introduced during the PEG extends into this space (Figure 5). Thus, the sella is not really empty, but is occupied by the pituitary gland and subarachnoid space. Many conditions, including perfectly normal endocrine states may be associated with an "empty sella."[13] The incidence of subarachnoid space observed extending into the sella radiologically in our series is less than that seen anatomically in a random autopsied population;[14] thus this finding has no specificity for acromegaly.

Laboratory Studies

While physical symptoms and signs and radiological findings are helpful, the definitive diagnosis of acromegaly is best made in the laboratory. The finding of an increased level of the fasting human growth hormone (HGH), which is not suppressible by glucose,[15] is the most definitive means of diagnosing acromegaly. We therefore measure HGH both after fasting and one hour after 100 gm of oral glucose. Acromegalic patients have HGH which is usually above 10 mμg per ml and does not suppress after glucose. In 20 percent of our patients a rise in HGH was seen after oral glucose. Non-acromegalic subjects, especially premenopausal women, may have elevations of HGH above the normal value of 5 mμg per ml with stress, prolonged fasting, anxiety or exercise; but one hour after ingestion of 100 grams of glucose, HGH decreases to less than 1 mμg per ml. The elevation of fasting HGH and its non-suppressibility by glucose may result from the secretion of excessive hypothalamic growth hormone releasing factor (GHRF), although this factor has not yet been measured directly.[16]

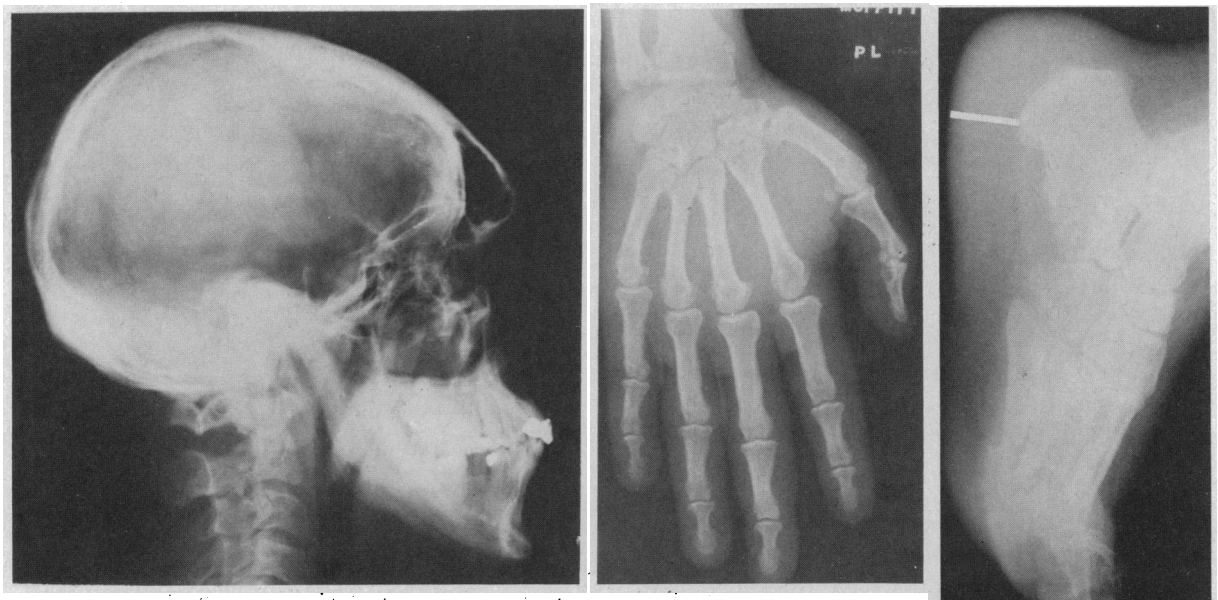

Figure 4.—Radiological signs in acromegaly. *Left*, skull, showing enlarged sella and frontal sinuses, hyperostosis frontalis interna, and enlarged mandible. *Center*, hand, with enlarged sesamoid bone and increased soft tissue shadows. *Right*, thickened heel pad, white line showing the distance measured.

The diurnal pattern of HGH secretion in normal subjects and in acromegalic patients is strikingly different.[17-20] Normally, morning values are less than 5 mμg per ml in the recumbent, fasting state, and there is an early fall after meals. Three to four hours after meals there may often be a small rise in HGH (3 to 8 mμg per ml) in ambulatory subjects. At night, 45 to 90 minutes after falling asleep, normal subjects have a considerable rise in HGH which is often as high as 10 to 35 mμg per ml. The peak level occurs when the electroencephalogram (EEG) sleep pattern is associated with nonrapid eye movements, and this level of HGH can be altered by changing sleep cycles.[21]

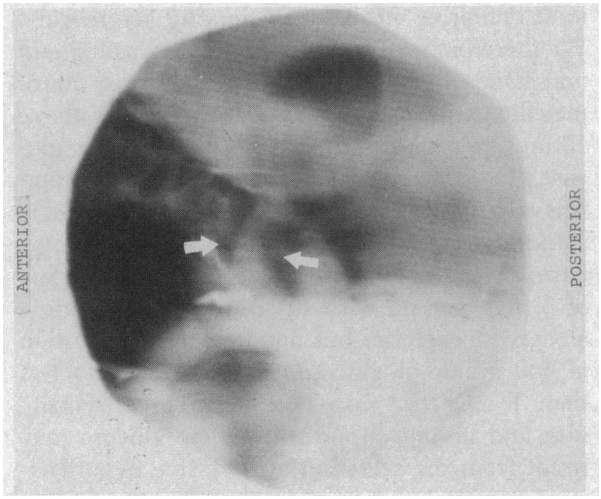

Figure 5. — Pneumoencephalogram showing an "empty sella" in a patient with acromegaly. White arrows show air anterior and posterior to the pituitary gland.

In contrast to normal subjects, the acromegalic patient has high HGH levels which do not vary consistently with meals or sleep. This chronic, nonrhythmic secretion of high levels of HGH results in the physical and metabolic changes characteristic of acromegaly.

The metabolic effects of HGH may occur only when the structure of the hormone is altered to form "sulfation factor".[22,23] This factor, when exposed to rachitic rat cartilage *in vitro*, will increase the uptake of radioactive sulfur, thymidine,[24] and proline[25] by the tissues, thereby reflecting growth of cartilage. Unaltered HGH instilled directly into the cartilage preparation *in vitro* will not cause increased sulfur uptake.

In addition to measuring HGH after a glucose load, the glucose tolerance test and serum immunoreactive insulin provide excellent means of following the patient's acromegalic status with relationship to the effect on carbohydrate metabolism. Preoperatively, we have observed hyperinsulinism in 66 percent of our patients in the presence or absence of an abnormal glucose tolerance test. An effect of HGH as a peripheral insulin antagonist has been suggested and re-

lated to increased lipolysis and free fatty acid oxidation subsequently interfering with glycolytic pathways.[23,26,27,28] Although direct insulinotropic actions of HGH have not been demonstrated *in vitro*, effects on insulin secretion may be involved in hyperinsulinism observed in acromegaly. When HGH levels are reduced, most patients have a concomitant improvement in glucose tolerance and lowering of insulin levels.

Assessment of adrenal and thyroid function should be undertaken in the acromegalic patient. To test adrenal function the metyrapone[29] and insulin hypoglycemia tests[30,31] are useful. Thyroid function is evaluated using the total thyroxine levels, T_3 uptake, and radioactive iodine uptake. In most instances, thyroid and adrenal function are found to be normal in acromegaly.

Recently, in collaboration with Drs. A. Charro and S. Friedman, we have measured gonadotropin levels using radioimmune assays for luteinizing hormone (LH) and follicular stimulating hormone (FSH). Using clomiphene citrate, an inhibitor of estrogen activity which results in stimulation of hypothalamic releasing factors and subsequent pituitary gonadotropin secretion, we have studied LH and FSH in acromegaly.[32] It had been thought formerly that in acromegaly gonadotropin secretion was deficient as a result of tumor expansion. Yet, in ten of twelve male patients with acromegaly and decreased libido the basal levels of LH and FSH were normal, and these levels increased normally during clomiphene administration. However, basal testosterone levels were low and response to increased endogenous gonadotropins was impaired. Thus, the gonadal testosterone response to gonadotropins, but not the gonadotropin levels, is reduced in acromegaly. The mechanism for this low testicular output of testosterone is unknown but may relate to an atypical structure of LH or FSH or both; or it is due to interference by HGH of testicular biosynthetic or secretory processes.

Occasionally other endocrine diseases are found with acromegaly. In our series of 50, we have seen four patients with thyroid nodules, two patients with hyperparathyroidism and one patient with Graves' disease.

Therapy

A recent mortality study of 194 patients by Wright et al[33] showed that after 45 years of age the annual death rate in patients with acromegaly was two to three times greater than in the normal population. Furthermore, the mortality rate was even greater in those patients with clinical diabetes. The most frequent causes of death were related to cardiovascular, cerebrovascular and respiratory diseases. The mortality rate in patients who had received some forms of treatment for acromegaly was less, thus documenting the need for treatment of this chronic disease.

TABLE 4.—*Acromegaly Treatment Used Today*

1. Irradiation
   a) Conventional Radiotherapy (34, 35, 36)
   b) Implants: Yttrium^{90}, gold^{198} (37)
   c) Heavy particle; proton beam; alpha particle (38, 39)
2. Surgical
   a) Craniotomy (40)
   b) Transsphenoidal, direct vision (41)
   c) Stereotaxic
      1) Cryosurgery (42, 43, 44)
      2) Radiofrequency (45)
      3) Ultrasonic (46)
3. Medical
   a) Medroxyprogesterone (47, 48)
   b) Chlorpromazine (49)

The various forms of treatment are shown in Table 4 with accompanying references.[34-49] The treatment used at the University of California, San Francisco, is cryohypophysectomy. Reduction in HGH levels is observed within a few days after cryosurgical treatment, whereas after radiation months or years may pass before low levels are attained. Metabolic responses to cryohypophysectomy are seen within a few weeks after operation.[50] Of the surgical approaches, the stereotaxic (that is, use of radiological guidance in performing the procedure) methods avoid craniotomy and extensive manipulation of brain tissue.

Experience with medroxyprogesterone as a medical means of reducing HGH has provided interesting new possibilities, but results have varied. The efficacy of chlorpromazine, an inhibitor of HGH responses in normal men (probably by acting upon hypothalamic pathways), remains to be evaluated in acromegaly.

Transsphenoidal cryohypophysectomy, as performed by Drs. John Adams and Robert Seymour of the University of California, San Francisco, Department of Neurosurgery, consists of the pas-

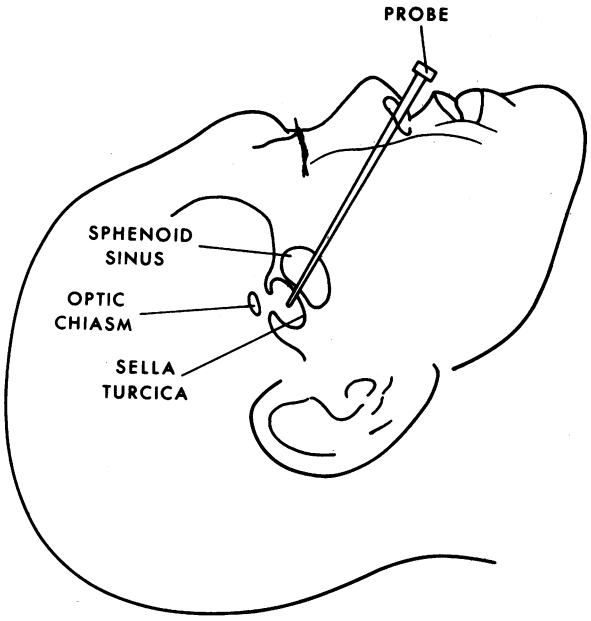

Figure 6.—Diagram of transsphenoidal surgical approach to pituitary gland with the cryohypophysectomy probe.

sage of a probe through the sphenoid sinus into the sella turcica (Figure 6) with subsequent placement of lesions in the pituitary by cold injury. This is done with lateral image intensifier and anterior-posterior polaroid x-ray guidance. Local anesthesia is used so that vision and eye movements can be evaluated throughout the procedure. Biopsy material also can be obtained through the probe. Pronounced suprasellar extension, as observed on pneumoencephalography, is a relative contra-indication to this form of surgical treatment, since cold injury might be conducted to the optic nerve.

Eighty-two percent of our 50 patients have been followed at least one year after operation. Drs. Nathan Becker, Fred Hofeldt and Victor Schneider collaborated in the evaluation of these patients who were in hospital at the General Clinical Research Center. Several endocrine and metabolic abnormalities may occur after treatment. During the first postoperative week there are alterations in water balance which are often predictable as to time and are triphasic in sequence. A diabetes insipidus syndrome occurred in one-third of our patients within the first 48 postoperative hours. This usually subsided; then during the fourth to sixth postoperative days hyponatremia occurred in one-fifth of the patients.[51] This condition is associated with a positive water balance and is best treated by water restriction. The concentration of sodium in the urine may be normal or high, and the syndrome appears to be primarily related to an inappropriate secretion of antidiuretic hormone (ADH). In two of the 50 patients a clinical picture of diabetes insipidus, which could be treated with chlorpropamide,[52] occurred on the eighth to tenth postoperative day. Thus, a triphasic sequence of altered water balance (consisting of an early ADH deficiency syndrome, then excessive release of ADH, and finally the late appearance of ADH deficiency) may occur after pituitary operation.[53] We have never observed all three phases to occur in the same patient. These changes have been described in humans after head injuries[54] and stalk sections[53] and in experimental animals after hypophysectomy.[55]

Other short and long term complications of cryohypophysectomy for acromegaly are seen in Table 5. Of interest is the fact that the procedure appears to reduce the release of HGH without causing hypopituitarism in the majority (88 percent) of patients.

Beneficial effects may be observed as early as the first postoperative week, when the patient notes less bulk in hand and facial tissues. During the ensuing weeks and years many symptoms subside in association with the reduced level of HGH. We have considered optimal response to be a fall in HGH level to less than 10 mμg per ml. We have correlated the extent of HGH changes with improvement of symptoms (Table 6). Most symptoms are improved to a greater degree in patients whose HGH levels decrease to less than 10 mμg per ml after treatment. Improvement in some symptoms, such as fatigue, headache and arthralgias, could not, however, be correlated with the level of HGH. Reversal of cosmetic alterations can be expected to occur only in those cases which are diagnosed and treated early in the course of the disease. Although soft tissue enlargement can be reduced, bony and cartilaginous changes show only minimal improvement.

The mean fasting HGH before cryosurgical operation in our 50 patients was 52 mμg per ml. Postoperatively, at most recent follow-up examinations (eight patients at six weeks, 17 patients at one year, 11 patients at two years, 11 patients at three years, three patients at four years), the mean fasting HGH was 16.8 mμg per ml. The majority of patients (76 percent) have postoperative

TABLE 5.—*Complications of Cryohypophysectomy*

	Incidence/Total Patients	
First 10 postoperative days		
Diabetes insipidus	10/50	Transient
Hyponatremia	5/26	Transient
Optic problems	9/50*	Transient
CSF rhinorrhea	3/50	Transient
Meningitis	2/50	(D. pneumonia)
Deaths	None	
Late postoperative period (over 6 weeks)		
Adrenal insufficiency	6/50	
Hypothyroidism	5/50	
Diabetes Insipidus	2/50	

*7 patients with paralysis of extraocular muscles, 2 patients with visual field defects.

TABLE 6.—*Relationship of Alteration of Symptoms to Postoperative Growth Hormone Level**

	Postoperative HGH (mμg/ml)	
	<10 mμg/ml	>10 mμg/ml
Acral Changes	53%	33%
Excessive Perspiration	72%	58%
Decreased Libido	33%	0%
Amenorrhea	29%	0%
Photophobia	31%	0%
Fatigue	33%	33%
Headaches	50%	55%
Arthralgias	56%	55%

*Values indicates percentage of patients with particular symptom that improved following cryohypophysectomy.

HGH less than 10 mμg per ml. Before operation 44 percent of the patients had an abnormal oral glucose tolerance test, while 8 percent had overt clinical diabetes. At our recent follow-up examination after operation only 28 percent of the patients had an abnormal glucose tolerance test, but all 8 percent still had overt clinical diabetes, although milder than it was preoperatively. The incidence of hyperinsulinemia was reduced in most patients as well.[56]

In summary, the classical appearance of a patient with far-advanced acromegaly makes the diagnosis easy. The challenge to physicians, however, is to detect and treat the disease before cosmetic, metabolic, and vascular changes are far advanced. Using a practical and precise method of measuring HGH before and after a glucose load allows such early detection of the disease.

Cryohypophysectomy is a form of treatment which alters the metabolic derangements in acromegaly, often without interfering with other pituitary functions.[57] At present this procedure appears to be a rapid, safe, and effective means of lowering HGH levels and thereby improving or preventing many of the clinical and metabolic disorders observed in acromegaly.

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THE OPHTHALMOLOGIST IN DIABETES

When do you think we as internists should send our diabetic patients to an ophthalmologist for evaluation?

I think that any patient who shows diabetic retinopathy of any extent should be sent to an ophthalmologist for complete evaluation of the fundus. If the internist who is following the patient for the diabetes is not accustomed to dilating the pupil once in a while for a fairly complete evaluation of the fundus, then I think that any person who has had diabetes for 10 years or longer, regardless of whether anything is seen in the fundus, should be sent to an ophthalmologist. A patient who is developing other complications, other vascular complications from their diabetes, either nephropathy or neuropathy, deserves a very thorough evaluation of the fundus. I think this is more important today than ever because we now realize that there is something that can be done for these people if they are seen early enough. Although we don't understand the exact mechanism of the pathogenesis, we do know enough about the evolution of the disease process to know that if it can be blocked at certain stages, the horrors that we see can sometimes be prevented. So in answer to the question once again, any patient who shows any degree of diabetic retinopathy should be evaluated by an ophthalmologist.

—EDWARD OKUN, M.D., St. Louis

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